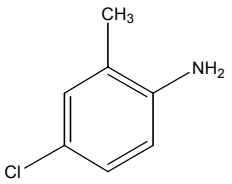
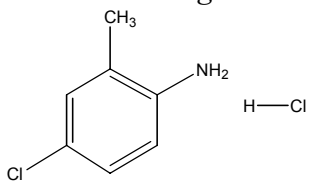
p-CHLORO-*o*-TOLUIDINE and *p*-CHLORO-*o*-TOLUIDINE HYDROCHLORIDE
CAS Nos. 95-69-2 and 3165-93-3

First Listed in the *Eighth Report on Carcinogens*



p-Chloro-*o*-toluidine



p-Chloro-*o*-toluidine hydrochloride

CARCINOGENICITY

p-Chloro-*o*-toluidine and its hydrochloride salt are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and evidence of malignant tumor formation in experimental animals (reviewed in IARC V.48, 1990).

There is limited evidence for the carcinogenicity of *p*-chloro-*o*-toluidine in humans. Documented human exposure has occurred primarily in the dye and synthetic chemistry industries. Between 1982 and 1990, 7 cases of urinary bladder cancer were detected in a group of 49 workers producing the insecticide chlordimeform from *p*-chloro-*o*-toluidine on an irregular basis for an average of 18 years. The incidence of bladder tumors in this group was significantly higher than that of the cancer registers. Exposure levels were not documented, but from 1980 to 1986, exposure to *p*-chloro-*o*-toluidine was analytically checked by monitoring of urine and was found to be minimal (quantitation of exposure not given). Increased incidences of tumors were observed primarily in the urinary bladder, and 1 of the 7 workers that had bladder cancer also developed a brain tumor. There was some evidence that the cohort studied handled other chemicals (including 4-chloroaniline); however, none of the resulting exposures were quantified by chemical analysis at the time (Popp et al., 1992). In other studies, workers were exposed to *p*-chloro-*o*-toluidine and numerous other compounds, several of which are known or possible carcinogens. Levels of exposure to all compounds were undocumented and occurred prior to the implementation of modern industrial hygiene standards in 1980 (Ott and Langer, 1983, cited by IARC V.48, 1990; Stasik, 1988; Hogan, 1993).

A significant increase of hemangiosarcomas or hemangiomas was observed in both sexes of two strains of mice on chronic administration of *p*-chloro-*o*-toluidine hydrochloride in the diet. *p*-Chloro-*o*-toluidine hydrochloride, however, was not a carcinogen when administered chronically in the diet of both sexes of two strains of rats (Weisburger et al., 1978; NCI 165, 1979).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

p-Chloro-*o*-toluidine has been demonstrated to be genotoxic in a variety of prokaryotic and mammalian *in vitro* and *in vivo* test systems (IARC V.48, 1990). *p*-Chloro-*o*-toluidine binding to DNA was demonstrated *in vitro* with calf thymus DNA (Bently et al., 1986) and *in vivo* when it was administered by intraperitoneal injection to rats (Hill et al., 1979; cited by IARC V.48, 1990).

No data are available that would suggest that the mechanisms thought to account for tumor induction by *p*-chloro-*o*-toluidine in mice would not also operate in humans.

PROPERTIES

p-Chloro-*o*-toluidine occurs in the form of leaflets (from ethanol). It has a boiling point of 241 °C and a melting point of 29-30 °C. It is soluble in hot alcohol and sparingly soluble in water, ethanol, and dilute acids. *p*-Chloro-*o*-toluidine hydrochloride occurs as a buff-colored powder or a light-pink powder. When heated to decomposition, *p*-chloro-*o*-toluidine and *p*-chloro-*o*-toluidine hydrochloride emit toxic fumes of nitrogen oxides (NO_x) and chlorine.

USE

p-Chloro-*o*-toluidine and its hydrochloride salt have been used commercially to produce azo dyes for cotton, silk, acetate, and nylon and as intermediates in the production of Pigment Red 7 and Pigment Yellow 49. As an azoic diazo component, *p*-chloro-*o*-toluidine is used in the synthesis of some azoic dyes, which are made by a two-step process involving diazotization of a primary amine component and coupling of the diazotized amine with a naphthol-derived coupling component (IARC V.48, 1990; NCI 165, 1979). *p*-Chloro-*o*-toluidine has also been used in the manufacture of the pesticide chlordimeform (IARC V.48, 1990).

p-Chloro-*o*-toluidine is also an impurity in (as the hydrochloride salt) and a metabolite of chlordimeform, which is an insecticide and acaricide. It has been used in the production of chlordimeform since the 1960s (IARC V.30, 1983; IARC V.48, 1990).

PRODUCTION

Commercial production of *p*-chloro-*o*-toluidine began in Germany in 1924 and was first reported in the United States in 1939 (IARC V.48, 1990). The USITC reported that 89,753 lb of *p*-chloro-*o*-toluidine and *p*-chloro-*o*-toluidine hydrochloride were imported in 1980, 83,098 lb in 1981, 31,747 lb in 1982, and 44,147 lb in 1983 (USITCa, 1981-1984). An IARC Working Group reported that production of *p*-chloro-*o*-toluidine in the United States stopped in 1979, and all importation and distribution of the compound were discontinued in 1986 (IARC V.48, 1990). Chem Sources (1996) identified eleven U.S. suppliers of *p*-chloro-*o*-toluidine and four U.S. suppliers of *p*-chloro-*o*-toluidine hydrochloride.

EXPOSURE

The routes of potential human exposure to *p*-chloro-*o*-toluidine and *p*-chloro-*o*-toluidine hydrochloride are inhalation, ingestion, and dermal contact. *p*-Chloro-*o*-toluidine may be found in the environment as a decomposition product of chlordimeform. The compounds are not known to occur naturally. Occupations with the greatest potential for exposure include pigment manufacturers and dyemakers and manufacturers of chlordimeform. Exposures to *p*-chloro-*o*-toluidine have been reported to occur during the charging of mixing vats and at the basification stage in a purification plant in England, by inhalation and dermal contact at a batch-operated chemical processing plant in the United States, and during production and processing at a plant in

the Federal Republic of Germany. Data on exposure levels were not provided for any of these studies (IARC V.48, 1990).

p-Chloro-*o*-toluidine has been isolated and identified in field samples of plant materials treated with chlordimeform, a pesticide, in young bean leaves at concentrations of less than 0.1 to 0.2 ppm, in grape stems at 0.02-0.3 ppm, in a mixture of grape stems and berries at 0.02-0.05 ppm, and in prunes and apples at less than 0.04 ppm. The compound was also reported to be formed from chlordimeform by enzymes present in the leaves of apple seedlings and in cotton plants (IARC V.48, 1990).

In an experimental field application, residue concentrations of *p*-chloro-*o*-toluidine were found in rice grains at 3-61 ppb, in straw parts at 80-7200 ppb, in the upper 0-5 cm layer of soil at 2-68 ppb, and in the lower 5-10 cm of soil at trace to 20 ppb. In another experimental field application, residues of the compound were not detected in rice grains or husks (IARC V.48, 1990).

p-Chloro-*o*-toluidine has been found in the urine of workers exposed to chlordimeform. It is a major metabolite of chlordimeform in dogs, rats, and goats (IARC V.48, 1990).

The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 1397 workers were potentially exposed to *p*-chloro-*o*-toluidine in the workplace (NIOSH, 1976). The National Occupational Exposure Survey (1981-1983) indicated that 250 workers (all women) were potentially exposed to *p*-chloro-*o*-toluidine, and 682 workers, including 425 women, were potentially exposed to *p*-chloro-*o*-toluidine hydrochloride (NIOSH, l990).

REGULATIONS

EPA regulates *p*-chloro-*o*-toluidine hydrochloride under the Resource Conservation and Recovery Act (RCRA); Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA); Superfund Amendments and Reauthorization Act (SARA); and the Toxic Substances Control Act (TSCA). *p*-Chloro-*o*-toluidine hydrochloride is subject to the reporting requirements of Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) and Section 6607 of the Pollution Prevention Act of 1990 (PPA). Section 313 of EPCRA, also referred to as Title III of the Superfund Amendments and Reauthorization Act of 1986 or SARA 313, requires the annual reporting, to EPA and the States, of releases and waste management activities for all listed chemicals manufactured, processed, or otherwise used in amounts exceeding threshold quantities by covered facilities. *p*-Chloro-*o*-toluidine is regulated under TSCA. EPA has established rules for regulating hazardous spills and requirements for handling and disposal of wastes. *p*-Chloro-*o*-toluidine hydrochloride is regulated as a hazardous constituent of waste under RCRA and is subject to report/recordkeeping requirements under RCRA and SARA. A statutory reportable quantity (RQ) of 1 lb (0.454 kg) was established for *p*-chloro-*o*-toluidine hydrochloride, but EPA increased the RQ to 100 lb (45.4 kg) under CERCLA. TSCA subjects both compounds to reporting requirements applicable to any significant new use. OSHA regulates *p*-chloro-*o*-toluidine and *p*-chloro-*o*-toluidine hydrochloride under the Hazard Communication Standard and as a chemical hazard in laboratories. The Department of Transportation (DOT) has its own regulations concerning the transportation of *p*-chloro-*o*-toluidine hydrochloride. Regulations are summarized in Volume II, Table B-26.